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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,131	GOLDSPINK, GEOFFREY	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-35,40-42,51,58-62,67-69 and 78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-35,40-42,51,58-62,67-69 and 78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/5/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Applicant's response to the First Action on the Merits was filed April 1, 2005. Claims 31, 58 have been amended, claims 1-30, 36-39, 43-50, 52-57, 63-66, 70-77, and 79-96 have been cancelled. Claims 31-35, 40-42, 51, 58-62, 67-69, and 78 are pending.

With regards to the Applicant pointing out that claim 40 had been withdrawn from consideration and yet had been considered by the Examiner in the First Office Action (November 4, 2004) (see Applicant's response, April 1, 2005, page 4, 2nd parag. under Remarks), the Applicant asserts that claim 40 had been withdrawn by mistake. The Examiner agrees with the Applicant that claim 40 is closely related to the subject matter of claim 31 from which claim 40 depends and thus, claim 40 should be under consideration.

Applicant is reminded that as a result of the restriction requirement filed February 18, 2004, the scope of analysis for the instant invention is limited to a method of treatment of an animal comprising administering a plasmid vector comprising a myosin light chain enhancer and a viral promoter operatively linked to a sequence that generates a therapeutic RNA. Claims which contain embodiments beyond this scope were not considered as part of the analysis.

Withdrawn Rejections

35 U.S.C. § 112, 1st paragraph-Enablement and Written Description

The rejection of claims 31, 32-35, 40-42, 49-51, 58-62, 67-69, and 76-78 under 35 U.S.C. 112, 1st paragraph-Enablement and Written Description has been withdrawn. Applicant has amended the claims such that the claims do not encompass "therapeutic RNA" as it reads on RNA molecules such as RNAi, ribozymes, and antisense.

While Applicants have overcome this 35 U.S.C. § 112, 1st paragraph-Enablement and Written Description rejection, the Examiner has new grounds of rejection for claims 31, 32-35, 40-42, 49-51, 58-62, 67-69, and 76-78 35 U.S.C. § 112, 1st paragraph-Enablement (see below).

35 U.S.C. §102(a)

The rejection of claims 31, 32-35, 40-42, 49-51, 58-62, 67-69, and 76-78 under 35 U.S.C. §102(a) as anticipated by Novo et al. (1997, Gene Therapy, 4: 488-492) is withdrawn. Applicants have pointed out that that Novo et al. was published May 2, 1997 and the present application claims benefit of Great Britain Patent Application No 9708526.0, filed April 25, 1997. The priority date of the instant application predates that of Novo et al.

The rejection of claim 31 under 35 U.S.C. §102(a) as anticipated by Ohshima et al. (1997, PNAS, 94: 2540-2544; published March 1997) is withdrawn. Applicants have submitted a Declaration of Dr. Goldspink under 37 C.F.R. § 1.131, wherein Dr. Goldspink states that the date of Exhibit I, a copy of a draft manuscript, describing the instant invention, was dated prior to March 1997 (Dr. Goldspink declaration, page 1, point 4). Dr. Goldspink's declared date predates that of Ohshima et al.

35 U.S.C. §102(b)

The rejection of claim 31 under 35 U.S.C. § 102(e) as anticipated by Weiner et al. is withdrawn. Applicants have pointed out that Weiner does not describe the use of vectors which include either a myosin heavy chain promoter or a viral promoter in combination with a myosin light chain enhancer to control expression of a therapeutic protein. The examiner finds the Applicants' argument persuasive.

35 U.S.C. § 103(a)

The rejection of claims 35, 40, 62, and 67 under 35 U.S.C. § 103(a) is withdrawn. Applicants have pointed out that there would have been no motivation to combine the teachings of Steffy and Weir, Donoghue, and Weiner, nor would there have been a reasonable expectation of success. The examiner finds the Applicants' arguments persuasive.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-35, 40-42, 51, 58-62, 67-69, and 78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s)

contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claims 31-35, 40-42, 51, 58-62, 67-69, 78 are drawn to a method of treatment of a human or an animal, wherein said method comprises administering an effective, non-toxic amount of a pharmaceutical composition comprising a vector comprising an expression cassette comprising a nucleic acid sequence encoding a polypeptide of

therapeutic use operably linked to a myosin heavy chain promoter and a myosin light chain enhancer.

At the time of filing, successful use of gene therapy was not routinely obtainable by those skilled in the art. W. French Anderson (1998, Nature, 392: 25-30), one skilled in the art, recently concluded: "(e)xcept for anecdotal reports of individual patients being helped, there is no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease (Anderson, page 25, 1st col., 1st parag., lines 9-11)." "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered. The reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how *in vivo* immune defenses can be overcome, and how to manufacture efficiently the vectors that we do make (Anderson, page 30, 1st col., 1st parag. under "Conclusions")." Concurring with Anderson, Verma and Somia (1997, Nature, 389: 239-242) state that "(t)he Achilles heel of gene therapy is gene delivery...and (t)hus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...(nonviral gene therapy approaches) suffer from poor efficiency of delivery and transient expression of the gene" and that "(a)lthough there are reagents that increase the efficiency of delivery, transient expression of the transgene is a conceptual hurdle that needs to be addressed (Verma and Somia, page 239, 3rd col., 2nd parag.)." "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single

outcome that we can point to as a success story (Verma and Somia, page 239, 1st col., 2nd parag.)."

In view of the failures associated with attempts to treat diseases by gene therapy as taught by Anderson and Verma and Somia, gene therapy should only be considered predictable in not being shown to work. Therefore, the need for working examples is particularly pronounced. The claimed invention broadly encompasses a method of treating a human or an animal comprising any diseases and any symptoms of a disease, wherein the human or animal is administered a pharmaceutical composition comprising an expression cassette operably linked to a myosin light chain enhancer, a viral promoter, and a polynucleotide sequence encoding a polypeptide of therapeutic use. However, the instant specification does not provide any working examples supporting a method for treating any diseases or any symptoms of a disease. The instant specification does demonstrates a mouse model of Fabry's disease wherein the mouse was injected with nucleic acid constructs (pX61 and pX62, pX4F, and pX7F) (specification, page 15, "Transfer of the alpha-galactosidase gene into a mouse model of Fabry's disease") and the activity of alpha-galactosidase in the muscles of the mice was assayed after one week or three weeks (specification, page 16, 1st parag.). While the specification teaches the activity levels of alpha-galactosidase in the Fabry disease mice, the specification does not teach that injection of the constructs had any salubrious effects on the mice. Nothing in the specification teaches that any of the alpha-galactosidase expressed in the mice alleviated any symptoms of Fabry's disease. The instant specification does not provide any working examples supporting a method for

treating Fabry's disease. Importantly, the working examples provided do not provide a nexus between expression of alpha-gal in cultured cells (e.g. Figure 4) or mice (Figure 5, see also specification, pages 15-16) and treatment of Fabry's disease. For example, there is no evidence of record suggesting that the levels of alpha-galactosidase observed following intramuscular injection in either C57BL/6 mice or in a Fabry's disease alpha-galactosidase knockout mouse model (see Fig. 5 and specification pages 15-16) carry any functional significance (or predictive value) relative to treatment of Fabry's disease in humans or animals. Crystal (1995, Science, 270: 404-410) has previously noted that "(h)umans are not simply large mice. There have been several surprise examples, in which predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials (Crystal, page 409, 1st col., see under "Humans are not simply large mice"). The specification does not provide sufficient guidance teaching the requisite protein levels of alpha-galactosidase for a therapeutic effect, nor does it provide any evidence that therapeutic alpha-galactosidase expression levels were either obtained or reflected in the reported expression levels recited on page 16 of the specification. In addition, the specification does not provide any guidance concerning the dosages of vector used in the knockout mouse model or any predictive correlation between intramuscular vector dose and the resulting levels and persistence of alpha-galactosidase expression.

Regarding intramuscular injection of DNA expression vectors, McCluskie et al. (1999, Molecular Medicine, 5: 287-300) concluded in a review of DNA vaccines that "no animal model may be ideal for prediction of efficacy in humans...(and) that the relatively

greater efficacy of IM in mice than primates may be related to morphological differences (or) (a)lternatively, it may be more related to dosage. The 10- to 100ug doses of DNA vaccine typically used in a 20g mouse would be equivalent to 35 to 35 mg in a 70kg human, a dose range greatly in excess of what has been used to date in human clinical trials (McCluskie et al. page 296, 2nd col., 3rd parag.)." The mere demonstration of alpha-galactosidase expression following intramuscular injection of 30 mg of pX7F in C57BL/6 mice (Figure 5) is not synonymous with appropriate delivery and expression levels of therapeutic genes so as to provide a therapeutic benefit, nor does it overcome the unpredictability in the art or sufficiently address the problems with gene therapy described by Anderson and Somia and Verma above, with regards to transient transgene expression as discussed above. In addition it should be noted that the 30 mg plasmid dose described in Figure 5 (specification, page 10,line 30) in a 20g mouse would be equivalent to a 105 gram dose in a 70kg human. This dose is greatly in excess of any dose ever used to date in a human clinical trial.

The claimed invention broadly encompasses a method of treatment for any disease. This includes neuronal disease. However, at the time of filing, the art teaches that direct gene transfer of plasmid DNA in muscle cannot be used to treat neuronal tissue. Dietz and Bahr, 2004, Molecular and Cellular Neuroscience, 27: 85-131 teach some of the hurdles an artisan would need to overcome in the art, in order for one to be able to use a non-viral vector effectively in a therapy. First, the protein of interest to be used to treat a neuronal disease would need to be sufficiently polar so that it can be well distributed within the organism. The protein of interest would also need to be

sufficiently hydrophobic to transverse the lipid bilayer of the cell (Dietz and Bahr, page 86, 2nd col., 1st parag. under "Delivery into cells and across the BBB—why Trojan horse trickery is in demand"). This criteria thus eliminates the broad scope that any polynucleotide sequence encoding a polypeptide of therapeutic use can be used in the claimed invention, wherein the protein is bound to the cell surface, is intracellular, or nuclear (see claim 31, step a and claim 58, step a). In short, secretable proteins would only be the set of proteins that can make its way from the muscle to a target organ and would fit Dietz and Bahr's criteria of a protein that could be sufficiently polar so that it can be well distributed within the organism. However, with regards to Dietz and Bahr's second criteria for a protein to be sufficiently hydrophobic to transverse the lipid bilayer, many secretable proteins are not hydrophobic, as they are soluble. In light of this issue, neither the specification nor the art teach how to make a soluble protein hydrophobic, such that it can transverse the lipid bilayer. The next hurdle, as pointed out by Dietz and Bahr, particularly for a neural protein, is that a protein needs to cross the blood-brain barrier. The art teaches that many proteins do not cross the blood-brain barrier (BBB) (e.g. a Google search using the search terms, "protein delivery BBB" brings up ArmaGen Technologies, a company that focuses on identifying ways to deliver neuronal proteins to the brain) and thus, many proteins with potential therapeutic value do not enter CNS drug development. As Dietz and Bahr and ArmaGen Technologies teach, protein delivery to the brain is not routine in the art. Nothing in the specification nor the art teach how to overcome this issue of enablement and thus, the claims are not enabled for this scope.

The claimed invention broadly encompasses a method of treatment for any disease. This includes diseases as varied as cancer, heart failure, and osteoperosis. While the claims broadly encompass treatment of any disease or any symptom of disease, the specification does not teach an artisan how to overcome two major hurdles in the art regarding administration of protein to effect therapeutic changes in an animal or human. The major hurdles that the art teaches are expression and delivery of the therapeutic protein. First, with regards to efficient expression, again referring to Dietz and Bahr, one major hurdle one needs to overcome in the art is efficient expression of the protein of interest from the DNA vector. The art at the time of filing teaches that naked plasmid DNA expression in muscle necessitates repeated injections of large amounts of DNA and low expression efficiency (Dietz and Bahr, page 86, 2nd col., under "Naked DNA"). Even after the DNA vector expresses protein, the specification does not teach that protein is produced in abundant amounts to have a therapeutic effect on any disease. Second, with regards to delivery of a protein of interest to a target site, the art teaches that one major problem encountered in both the human clinical trials and animal model studies was the virtual exclusive clearance of the administered enzyme by the liver. The art teaches that current modes of enzyme replacement therapy, involving the injection of an active forma of the enzyme into the body of an individual have several problems in addition to rapid clearance from the body. Repeated injections of enzyme derived from a heterologous species may lead to the subsequent development of a hypersensitivity reaction by the individual. Development of such an immune response by the individual may not only undesirably enhance the clearance of the

enzyme, but also may result in a clinically manifested, life-threatening reaction. Another problem is the potential for bio-inactivation of the administered enzyme by proteolytic enzymes found circulating in the bloodstream. To compensate for the rapid clearance from the body, or for bio-inactivation, and because the administered enzyme is not specifically targeted to cells containing the deficient enzyme activity, the active enzyme has been administered in quantities much greater than the body needs. This in turn may undesirably increase the chances of developing a hypersensitivity reaction (Allen, Jr., et al., U.S. Patent, 5,433,946, patented July 18, 1995, see col. 1, line 48 to col. 2, line 3). While the art teaches these hurdles that an artisan must overcome in order to enable an artisan to treat a disease, nothing in the specification teaches any method of how to administer a plasmid construct comprising a gene of interest, express the protein, and be able to effect therapy in a human or animal. Nothing in the specification teaches an artisan how to direct the therapeutic protein to the target site, how to reduce clearance of the protein by the liver, how to reduce the potential for bio-inactivation, or how to avoid an immune response of the body against the heterologous protein. As such, since no guidance was given, the specification at the time of filing does not enable an artisan to practice any method of treating any disease in a human or an animal body using a DNA plasmid comprised of an expression cassette comprising a myosin light chain enhancer, a viral promoter, and a nucleic acid sequence encoding any polypeptide of therapeutic use.

In view of the lack of guidance, working examples, and breadth of the claims, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-35, 40-42, 51, 58-62, 67-69, and 78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 41, 42, 68, and 69 are indefinite in their recitation of the phrase, "further comprising...genomic sequences flanking said expression cassette" since the expression cassettes implicitly comprise genomic sequences; thus it is not clear how the limitation further limits the base claim.

Claims 31 and 58 (and their dependent claims) are incomplete claims since the method steps do not clearly relate back to the preamble which recites a "method of treatment." The method steps do not recite an object to which the administration step is directed to, nor is there any recited step relating to "treatment." As used therein, the "method of treatment" merely recites an intended use and is accorded no patentable weight.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31-35, 40-42, and 51 are rejected under 35 U.S.C. 103(a) as obvious over Goldspink et al. (WO 94/28151, published December 9, 1994) in view of Jeang, et al. (1984, Molecular and Cellular Biology, 4: 2214-2223).

It is noted that the methods of claims 31-35, 40-42, and 51 are incomplete claims wherein the method steps do not clearly relate back to the preamble, for purposes of applying prior art, the intended use limitations recited therein are given no patentable weight. Further, the pharmaceutical composition of claim 31 and its intended use recites no physical limitation that would distinguish the claimed pharmaceutical composition from an otherwise identical composition. The recitation of "pharmaceutical" is a limitation of intended use and is therefore given no patentable weight.

Goldspink discloses a plasmid (pPRF8PAS-E9, page 10, line 24) comprising an expression cassette comprising, in operable linkage, a myosin light chain enhancer, a truncated rabbit β-cardiac myosin heavy chain promoter, and a polynucleotide of therapeutic interest further comprising at least one epitope (i.e.Factor VIII coding region). Goldspink further teaches that the constructs of the disclosed invention may be incorporated into a plasmid, virus, or phage vectors that would inherently comprise both mammalian and/or viral genomic sequences flanking the expression cassettes. Goldspink further discloses a method of administering by intramuscular injection in mice

of pPRF8PAS-E9 in an amount resulting in expression of Factor VIII (paragraph abridging pages 13-14).

While Goldspink teaches the vector comprising a truncated rabbit β-cardiac myosin heavy chain promoter, Goldspink does not teach a viral promoter.

Jeang et al. teaches that the IE94 gene of cytomegalovirus contains all of the regulatory elements necessary for strong constitutive expression in mammalian cells (Jeang, et al., 1984, Molecular and Cellular Biology, 4: 2214-2223, end of abstract). Jeang et al. also teach the characteristics of the IE94 promoter: "the 5' promoter region has a typical TATAA box at position –28 but that in addition, the upstream flanking sequence between positions –500 and –1300 comprises a remarkable and novel sequence arrangement including 24 tandem repeats of a basic 30-base-par element with central 19-base-pair palendromic structure that resembles multiple CAAT boxes. In addition, between –70 and –400, there occur 10 nonadjacent copies of a 16-base-pair palendromic element that is highly consderved between human and simian CMV IE promoters and may contribute to the strong, constitutive expression (Jeang, et al., page 2221, 2nd col., line 12 to page 2222, 1st col., 1st parag.)."

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the truncated rabbit β-cardiac myosin heavy chain promoter with the promoter from CMV IE94.

One having ordinary skill in the art would have been motivated to substitute these promoters, one for the other, in order to obtain an expression vector that expressed high levels of Factor VIII in mammalian muscle cells.

There would have been a reasonable expectation of success given Jeang et al. for teaching that the CMV IE94 gene was comprised of a promoter that contained all the regulatory elements necessary for strong constitutive expression in mammalian cells.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Claims 58-62, 67-69, 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldspink et al. (WO 94/28151, published December 9, 1994) in view of Fenjves et al., (1989, PNAS, USA, 86: 8803-8807) and Abdallah et al., (1995, Biol. Cell., 85: 1-7).

It is noted that the methods of claims 58-62, 67-69, 78 are incomplete claims wherein the method steps do not clearly relate back to the preamble, for purposes of applying prior art, the intended use limitations recited therein are given no patentable weight. Further, the pharmaceutical composition of claim 58 and its intended use recites no physical limitation that would distinguish the claimed pharmaceutical composition from an otherwise identical composition. The recitation of "pharmaceutical" is a limitation of intended use and is therefore given no patentable weight.

Goldspink discloses a plasmid (pPRF8PAS-E9, page 10, line 24) comprising an expression cassette comprising, in operable linkage, a myosin light chain enhancer, a truncated rabbit β-cardiac myosin heavy chain promoter, and a polynucleotide of therapeutic interest further comprising at least one epitope (i.e.Factor VIII coding region). Goldspink further teaches that the constructs of the disclosed invention may be incorporated into a plasmid, virus, or phage vectors that would inherently comprise both

mammalian and/or viral genomic sequences flanking the expression cassettes. Goldspink further discloses a method of administering by intramuscular injection in mice of pPRF8PAS-E9 in an amount resulting in expression of Factor VIII (paragraph abridging pages 13-14).

While Goldspink teaches that the invented vector can be used to express Factor VIII, Goldspink does not teach that other proteins can be expressed from the vector.

Fenjves et al. teach that human apolipoprotein E (apo E) was monitored in the circulation of athymic mice and rats bearing epidermal grafts. Human apoE was detected in the systemic circulation of graft-bearing animals as long as the graft remained on the animal. Within 24 hours of graft removal, human apoE was not detectable in plasma, indicating that apoE resulted from continuous production of the protein by grafted keratinocytes (Fenjves, et al., abstract). While Fenjves et al. do not teach the sequence of apoE, the sequence was available on GenBank since 1989 (GenBank gi number: 178850).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to insert the cDNA sequence of human apolipoprotein E into the expression plasmid taught by Goldspink.

One having ordinary skill in the art would have been motivated to make an expression vector comprising apoplipoprotein E so that apoE could be expressed in animals. Fenjves et al. teach that apoE was administered to mice and rats via a transplant. The art teaches that success of transplants of tissue and cells are unpredictable due to rejection cause by an animal's response system. Fenjves et al.

circumvented the problem of tissue rejection by using athymic mice and rats. Goldspink's vector has a great advantage over the system used by Fenjves et al. to administer apoE because Goldspink's vector can be administered without inducing immune responses in the animal. (The fact that non-viral systems induce lower immune responses is well known in the art, e.g. Abdallah, et al., 1995, Biol. Cell., 85: 1-7, see page 1, 1st col., 3rd parag.). Further, Goldspink's vector can be administered with one injection of DNA, while Fenjeves et al.'s system involves surgery.

There would have been a reasonable expectation of success given the results of Goldspink for teaching that the expression vector, pPRF8PAS-E9, expresses protein.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JH

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER